

WHAT IS CLAIMED IS:

1. A method for the preparation of a phosphorus-linked oligomer comprising the steps of:
 - (a) providing a solid support;
 - 5 (b) attaching a 5'-O-protected nucleoside to the solid support;
 - (c) deprotecting the 5'-hydroxyl of the nucleoside with a deprotecting reagent comprising a protic acid in a solvent to deprotect the 5'-hydroxyl of the nucleoside, the
10 solvent being an aromatic solvent, an alkyl aromatic solvent, a halogenated aromatic solvent, a halogenated alkyl aromatic solvent, or an aromatic ether solvent;
 - (d) reacting the deprotected 5'-hydroxyl with an 5'-protected activated phosphorus compound to produce a
15 covalent linkage therebetween;
 - (e) oxidizing or sulfurizing the covalent linkage to form a phosphodiester, phosphorothioate, phosphorodithioate or H-phosphonate linkage;
 - (f) repeating steps c through e at least once for
20 subsequent couplings of additional activated phosphorus compounds, to produce the completed phosphorus-linked oligomer; and
 - (g) cleaving the oligomer from the solid support.
2. The method of claim 1 further comprising the step
25 of capping remaining reactive sites with a solution containing a capping reagent.
3. The method of claim 1 wherein the oxidation or sulfurization step is performed after each iteration of steps (c) and (d).
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4. The method of claim 1 wherein the oxidation or sulfurization step is performed after the final iteration of steps (c) and (d).
5. The method of claim 1 wherein the solvent in step

(c) is an aromatic solvent, an alkyl aromatic solvent, or an aromatic ether.

6. The method of claim 1 wherein the solvent in step (c) is benzene, toluene, benzonitrile, o-, m- or p-xylene, 5 mesitylene, or diphenyl ether.

7. The method of claim 6 wherein the solvent in step (c) is benzene, toluene or o-, m- or p-xylene.

8. The method of claim 7 wherein the solvent in step (c) is toluene.

10 9. The method of claim 1 wherein the solvent in step (c) is a halogenated aromatic solvent or a halogenated alkyl aromatic solvent.

10. The method of claim 9 wherein the solvent in step (c) is chlorobenzene or benzotrifluoride.

15 11. The method of claim 1 wherein the activated phosphorus compound is an activated mononucleotide, an activated dinucleotide, or an activated polynucleotide.

12. The method of claim 1 wherein the activated phosphorus compound is a 5'-protected nucleoside 20 phosphoramidite or a 5'-protected activated H-phosphonate nucleoside.

13. The method of claim 1 wherein the protecting group of the 5'-O-protected nucleoside and the 5'-protected activated phosphite compound is independently trityl, 25 monomethoxy trityl, dimethoxytrityl, trimethoxytrityl, 2-chlorotrityl, DATE, TBTr, 9-phenylxanthine-9-yl (Pixyl) or 9-(p-methoxyphenyl)xanthine-9-yl (MOX).

14. The method of claim 13 wherein the protecting

group of the 5'-O-protected nucleoside and the 5'-protected activated phosphite compound is independently trityl, monomethoxy trityl, dimethoxy trityl, 9-phenylxanthine-9-yl (Pixyl) or 9-(p-methoxyphenyl)xanthine-9-yl.

- 5 15. The method of claim 14 wherein the protecting group of the 5'-O-protected nucleoside and the 5'-protected activated phosphite compound is dimethoxytrityl.

- 10 16. The method of claim 1 wherein the phosphorus-linked oligomer is a phosphodiester, phosphorothioate phosphorodithioate, or H-phosphonate oligonucleotide.

- 15 17. The method of claim 1 wherein the protic acid is formic acid, acetic acid, chloroacetic acid, dichloroacetic acid, trichloroacetic acid, trifluoroacetic acid, benzenesulfonic acid, toluenesulfonic acid, or phenylphosphoric acid.

18. The method of claim 1 wherein the solvent in step (c) further comprises an additive.

19. The method of claim 18 wherein the additive to the solvent in step (c) is an alcohol.

- 20 20. The method of claim 19 wherein the alcohol additive to the solvent in step (c) is from 0% to about 30% methanol, ethanol, 2-propanol, t-butyl alcohol, t-amyl alcohol, benzyl alcohol, or 1,1,1,3,3,3-hexafluoro-2-propanol, or a mixture thereof.

- 25 21. A method for the preparation of a phosphorus-linked oligomer comprising the steps of:
- a) providing a solid support;
 - b) attaching a 5'-O-protected nucleoside to the solid support;
 - 30 c) contacting the protected 5'-hydroxyl of the

nucleoside with a deprotecting reagent comprising a protic acid in a solvent to deprotect the 5'-hydroxyl of the nucleoside, the solvent being an aromatic solvent, an alkyl aromatic solvent, a halogenated aromatic solvent, a
5 halogenated alkyl aromatic solvent, or an aromatic ether solvent;

d) reacting the deprotected 5'-hydroxyl with a 5'-protected activated phosphite compound to produce a phosphite linkage;

10 e) oxidizing or sulfurizing the phosphite linkage to form a phosphodiester, phosphorothioate, or phosphorodithioate linkage;

f) repeating steps c through e at least once for subsequent couplings of additional activated phosphite
15 compounds, to produce the completed phosphorus-linked oligomer; and

g) cleaving the oligomer from the solid support.

22. The method of claim 21 further comprising the step of capping remaining reactive sites with a solution
20 containing a capping reagent.

23. The method of claim 21 wherein the solvent in step (c) is an aromatic solvent, an alkyl aromatic solvent, or an aromatic ether.

24. The method of claim 23 wherein the solvent in step
25 (c) is benzene, toluene, benzonitrile, o-, m- or p-xylene, mesitylene, or diphenyl ether.

25. The method of claim 24 wherein the solvent in step (c) is benzene, toluene or o-, m- or p-xylene.

26. The method of claim 25 wherein the solvent in step
30 (c) is toluene.

27. The method of claim 21 wherein the solvent in step

(c) is a halogenated aromatic solvent or a halogenated alkyl aromatic solvent.

28. The method of claim 27 wherein the solvent in step (c) is chlorobenzene or benzotrifluoride.

5 29. The method of claim 21 wherein the activated phosphite compound is a mononucleotide phosphoramidite, a dinucleotide phosphoramidite, or a polynucleotide phosphoramidite.

10 30. The method of claim 21 wherein the protecting group of the 5'-O-protected nucleoside and the 5'-protected activated phosphite compound is independently trityl, monomethoxy trityl, dimethoxytrityl, trimethoxytrityl, 2-chlorotrityl, DATE, TBTr, 9-phenylxanthine-9-yl (Pixyl) or 9-(p-methoxyphenyl)xanthine-9-yl (MOX).

15 31. The method of claim 30 wherein the protecting group of the 5'-O-protected nucleoside and the 5'-protected activated phosphite compound is independently trityl, monomethoxy trityl, dimethoxy trityl, 9-phenylxanthine-9-yl (Pixyl) or 9-(p-methoxyphenyl)xanthine-9-yl.

20 32. The method of claim 31 wherein the protecting group of the 5'-O-protected nucleoside and the 5'-protected activated phosphite compound is dimethoxytrityl.

25 33. The method of claim 21 wherein the phosphorus-linked oligomer is a phosphodiester, phosphorothioate or a phosphorodithioate oligonucleotide.

30 34. The method of claim 21 wherein the protic acid is formic acid, acetic acid, chloroacetic acid, dichloroacetic acid, trichloroacetic acid, trifluoroacetic acid, benzenesulfonic acid, toluenesulfonic acid, or phenylphosphoric acid.

35. The method of claim 21 wherein the solvent in step (c) further comprises an additive.

36. The method of claim 35 wherein the additive to the solvent in step (c) is an alcohol.

5 37. The method of claim 36 wherein the alcohol additive to the solvent in step (c) is from 0% to about 30% methanol, ethanol, 2-propanol, t-butyl alcohol, t-amyl alcohol, benzyl alcohol; or 1,1,1,3,3,3-hexafluoro-2-propanol, or a mixture thereof.

10 38. The method of claim 22 wherein the solvent in step (c) is benzene, toluene, benzonitrile, o-, m- or p-xylene, mesitylene, or diphenyl ether; the activated phosphite compound is a mononucleotide phosphoramidite, a dinucleotide phosphoramidite, or a polynucleotide phosphoramidite; the
15 protecting group of the 5'-O-protected nucleoside and the 5'-protected activated phosphite compound is dimethoxytrityl; the phosphorus linked oligomer is a phosphodiester, phosphorothioate or a phosphorodithioate oligonucleotide; and the protic acid is dichloroacetic acid.

20 39. The method of claim 38 wherein the solvent in step (c) is toluene.

40. The method of claim 39 wherein the activated phosphite compound is a mononucleotide phosphoramidite.

25 41. The method of claim 1 wherein the 5'-protected activated phosphorus compound is a 5'-protected activated H-phosphonate compound; and the phosphorus-linked oligomer is a H-phosphonate oligonucleotide.